Paediatric Trials – Daily Challenges in Clinical Practice

AGAH Workshop:
Critical Aspects of Integrated Drug Development –
Expect the Unexpected!

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Lack of Knowledge

So far, only a limited number of clinical trials has been performed in children.

This causes problems:

• In drug development planning
• Practical problems in paediatric clinical trials
Lack of knowledge about physiology in children:

Pharmacokinetic and pharmacodynamic differences between children of different age groups and adults concerning

- Body water
- Muscle and fat content
- Protein binding
- Renal and liver function
- Gastrointestinal tract
- Skin
- Blood-brain barrier
- Deglutition process

--> The unexpected: More different formulations and dose levels than expected might need to be developed for the different age groups.

Availability of scientifically sound clinical trials in topics of galenic paediatric development is limited
→ difficulty to decide on suitable trial designs and conditions

→ The unexpected:
  - Need to perform own exploratory studies.
  - Need to develop an own pharmacological model.
Lack of agreed standard therapies in different countries and even different hospitals for a specific indication concerning

- Substance
- Doses and dosing criteria
- Galenic formulations

→ Difficulty to decide on doses to be provided by a new galenic formulation

→ The unexpected: Need to establish a consensus process amongst paediatricians.
Time point of PIP development at the end of Phase I also means that few knowledge about galenic options for paediatric formulations is available:

1. Limited knowledge about broadly preferred type of galenic formulations amongst paediatricians for a specific disease, age group and drug

→ The unexpected: Need to establish a consensus process amongst paediatricians.

2. No knowledge about the effective dose range of a new substance neither in adults nor in children

→ The unexpected: Dose range too low or too high for the technical possibilities of the planned formulation especially for small children.
3. Limited knowledge about **technical options** for the development of a paediatric formulation → liquid, minitablet, spray, suppository, …

→ **The unexpected**: The planned formulation does not provide the required doses.
Paediatricians are used to administer *drugs adapted to body weight*

→ **The unexpected:**

- The planned fixed dose levels in all but liquid formulations are not sufficiently flexible, especially for the very small children.

- More flexibility through liquids, but exact administration is often unreliable.

- The level of required different formulations is beyond financial means and available timelines.
When medication with **high dose per body weight** is required, a **lot of volume in liquid or lots of minitablets** are necessary

→ **The unexpected:** The selected formulation is not suitable to be administered in sufficient multiples (e.g. several minitablets, unacceptably high volume of liquid, …).

**Dose levels** of the new drug need to be **investigated in all age groups**

→ **The unexpected:** No bioanalytical method available to detect the low doses to be expected, especially in very small children.
Administration to children is more complex than to adults: taste sensation is different in children and develops over age

→ The unexpected:

- The taste of the selected formulation is not acceptable to children of a respective age group.
- It might technically not be possible to mask the taste.
PDCO has a different view on the proposed PIP conditions concerning age groups to be covered, suitability of dosage forms, dosing flexibility required, …

→ The unexpected: PIP not accepted, need for more or other studies.

EMA has released a guideline on the development of paediatric galenic formulations

→ The unexpected: During preparation and negotiation of the PIP there is new knowledge developed through properly designed clinical trials that change the EMA guideline

A real life case…: Minitablets

Definition:

- No definition in Pharmacopoeias (Ph.Eur., USP, JP) or from Regulatory authorities
- In scientific literature the size is defined as “equal or smaller than 3 mm in diameter”

Advantages over **liquids**:  
- easier in handling  
- reliable in content uniformity and drug administration  
- safer concerning excipients  
- cheaper in production  
- better drug stability and storage conditions  
- precision of dosing

Advantages over **usual sized tablets**:  
- less swallowing and compliance problems (e.g. bad taste)  
- age adapted and reliable dosing  
- no need of crashing or dissolving
Paediatric Subpopulations

**Exploratory- and confirmatory study: 6 months – 6 years**

*ICH E 11 „Clinical investigation of medicinal products in the paediatric population“*

<table>
<thead>
<tr>
<th>Preterm newborn infants</th>
<th>Term newborn infants</th>
<th>Infants and Toddlers</th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 m</td>
<td>2 y</td>
<td>6 y</td>
<td>12 y</td>
</tr>
</tbody>
</table>

**CHMP reflection paper „Formulations of choice for the paediatric population“**

**Neonate study: 2 – 28 days**
Objectives and Rationale

• To determine the **acceptability** and the **swallowability** of small-sized solid dosage forms (**coated and uncoated minitablets**), 2 mm diameter) in comparison to glucose syrup 15% from neonates to pre-school children.

• These clinical studies were aimed at **generating valid data** on the acceptability of uncoated and coated drug-free minitablets in **children < 6 y**.
Drug-free formulation (Placebo):

- Minitablet uncoated ø 2 mm
- Minitablet coated ø 2 mm
- Glucose-Syrup 15%, 0.5 respectively 3 ml
Study Design

• 3 studies:

  ➢ **Exploratory study:** 60 patients aged 6 months – 6 years (uncoated minitablet, syrup)

  ➢ **Confirmatory study:** 306 patients aged 6 months – 6 years (uncoated and coated minitablet, syrup)

  ➢ **Neonate study:** 151 patients aged 2 – 28 days (uncoated minitablet, syrup)

• in total 517 patients aged 2 days – 5 years inclusive

• single-centre, open, randomised, single dose, cross-over design

• inhouse and outpatient paediatric patients
GCP Conformity

- Study performed according to Declaration of Helsinki and ICH-GCP
- Favourable opinion from the Ethics Committee of Düsseldorf University
- Studies registered in the German Clinical Trials Register
- Monitoring and data management performed by KKS Düsseldorf
- Written Informed Consent from both parents, and Assent from children received whenever possible
Examination Plan (I) (Confirmatory study)

- Written Informed Consent and Assent obtained
- In- and exclusion criteria assessed
- Randomisation to the sequence of placebo formulations according to the randomisation scheme
- Oral inspection
- Drug administration
  - either the uncoated minitablet with a drink of their choice
  - or the coated minitablet with a drink of their choice
  - or 3 ml of the glucose-syrup (teaspoon or pipette)
Examination Plan (II) (Confirmatory study)

- The process of deglutition was observed and the result of swallowing assessed by oral inspection.

- As soon as the child was ready for the 2nd resp. the 3rd part of the examination, the administration and assessment procedures were repeated with the other formulations.
## Evaluation Criteria (Confirmatory study)

<table>
<thead>
<tr>
<th>Coated and uncoated minitablet</th>
<th>Syrup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowed</td>
<td>Everything swallowed</td>
</tr>
<tr>
<td>Chewed</td>
<td>Small runlet or residuals</td>
</tr>
<tr>
<td>Spat out</td>
<td>Spat out</td>
</tr>
<tr>
<td>Choked on</td>
<td>Choked on</td>
</tr>
<tr>
<td>Refused to take</td>
<td>Refused to take</td>
</tr>
</tbody>
</table>
Results: Primary Objective
(Confirmatory study)

Acceptability: *uncoated* minitablet
> syrup
over all age groups
Difference 15,0 % (95 % CI 10,3-19,6)
p < 0.0001

(Secondary objective:

Acceptability: *coated* minitablet > syrup
over all age groups
Difference 14,9 %
(95 % CI 10,4-19,5)
p < 0.0001)

Results based on n=303 as 3 children refused to take any formulation
Results: Secondary Objective (Confirmatory study)

**Swallowability**

**Capability to swallow:**
- *uncoated* minitablet > syrup over all age groups
  - Difference 12.6% (95% CI 5.7-19.6)
  - *(p = 0.0007)*

- *coated* minitablet > syrup over all age groups
  - Difference 11.6% (95% CI 4.6-18.6)
  - *(p = 0.002)*

**Difference in acceptability and capability to swallow**
not significant between *uncoated* and *coated* minitablets

Results based on n=303 as 3 children refused to take any formulation
Examination Plan (I) (Neonate study)

- Written Informed Consent from both parents obtained
- In- and exclusion criteria assessed
- Randomisation to the sequence of placebo formulations according to the randomisation scheme
- Oral inspection
- Drug administration
  - either the uncoated minitablet with a drink of the parents choice
  - or 0.5 ml of the glucose-syrup (pipette)
Examination Plan (II) (Neonate study)

- The process of deglutition was observed and the result of swallowing assessed by oral inspection.

- As soon as the child was ready for the 2nd part of the examination, the administration and assessment procedures were repeated with the other formulation.
### Evaluation Criteria (Neonate study)

<table>
<thead>
<tr>
<th>Uncoated minitablet</th>
<th>Syrup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everything swallowed</td>
<td>Everything swallowed</td>
</tr>
<tr>
<td>Partially swallowed</td>
<td>Partially swallowed</td>
</tr>
<tr>
<td>Inhaled or coughed</td>
<td>Inhaled or coughed</td>
</tr>
<tr>
<td>Termination of the examination</td>
<td>Termination of the examination</td>
</tr>
<tr>
<td>by the parents</td>
<td>by the parents</td>
</tr>
</tbody>
</table>

Uncoated minitablet: Everything swallowed, Partially swallowed, Inhaled or coughed, Termination of the examination by the parents

Syrup: Everything swallowed, Partially swallowed, Inhaled or coughed, Termination of the examination by the parents
### Results (I) (Neonate study)

<table>
<thead>
<tr>
<th></th>
<th>Everything swallowed</th>
<th>Partially swallowed</th>
<th>Inhaled/ coughed</th>
<th>Termination by the parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>minitablets</td>
<td>124</td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>syrup</td>
<td>109</td>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Pre-term neonates** ($<37+0$ weeks of gestation): 11 of 151

<table>
<thead>
<tr>
<th></th>
<th>Everything swallowed</th>
<th>Partially swallowed</th>
<th>Inhaled/ coughed</th>
<th>Termination by the parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>minitablets</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>syrup</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Results (II) (Neonate study)

Primary objective: Acceptability
Minitablet = syrup
Difference 0 %

Secondary objective: Swallowability
Minitablet > syrup
Difference 9.9% (95% CI 1.4-19.3)
p=0.0000094
Results: Safety
(Exploratory, Confirmatory and Neonate studies)

• All three galenic formulations were well tolerated
• None of the children choked on the syrup
• None of the children choked on the uncoated minitablet
• 2 children (both in age group 0.5 - 1y) choked on the coated minitablet, both events without clinical relevance
• But: the number of patients and duration of application are not sufficient for reliable data on safety!
Conclusion from the Three Studies

• Acceptability of uncoated and coated minitablets were significantly superior to syrup over all age groups, particularly prominent in children between 1 and 4 years.

• Uncoated and coated minitablets are therefore suitable alternatives to liquid paediatric formulations for young children

• In neonates acceptability of uncoated minitablets and syrup was equally 100%, but swallowability was significantly higher in uncoated minitablets

• Uncoated minitablets are therefore suitable dosage forms for paediatric age groups as of preterm neonates

• Coated minitablets should be recommended for children older than 1 year
Future Projects

- Multiple minitablets per child per application
- Minitablets with active ingredients (palatability (e.g. taste), texture, etc.)
Subject selection for placebo containing formulation studies

→ The unexpected:

- The conditions for involvement of healthy children is different in different EU-Member states
- Clinical trials with placebo containing formulations may not fall under the national drug law
Informed consent process

- The unexpected:
  - Differences in requirement concerning the need for one or both parent signatures (e.g. problems with divorced parents)
  - The level of suspicion of parents against participating in clinical trials
Need to receive **Assent** as far as possible

→ The unexpected:

- Difficult to explain to children what to do (e.g. need for comic to be approved by the ethics committee and capability to explain the complex concept of a clinical trial to small children)

- Mismatch in willingness for study participation between child and parents

- Adolescents don‘t want to participate in clinical trials out of fear to be stigmatised for being sick
Lack of motivation and compliance in small children to administer the drug

→ The unexpected: Treatment might not be reliably measurable

Children have different preferences for administration vehicles (e.g. food, drinks, …)

→ The unexpected:

- Standardisation of administration may be more difficult or even impossible

- Food administration requirement may have to be labeled
Clinical trials in children require **liability insurance**

→ The unexpected: The insurance company can not correctly estimate the risk level leading to extremely high insurance fees
Thank you for your kind attention!